UNITED STA[redacted] DEPARTMENT OF COMMERCE
Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/234,290	01/20/99	BURKLY L	10274/008003

HM12/0309

LOUIS MYERS
FISH & RICHARDSON
225 FRANKLIN STREET
BOSTON MA 02110-2804

EXAMINER	
UNGAR,S	
ART UNIT	**PAPER NUMBER**
1642	14

DATE MAILED: 03/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/234,290	Applicant(s) Brukly
	Examiner Ungar	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Dec 15, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *25, 28, and 31-36* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *25, 28, and 31-36* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice To comply

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Amendment filed December 15, 2000 (Paper No. 11) in response to the Office Action of June 13, 2000 (Paper No. 9) is acknowledged and has been entered. New claim 36 has been added. Claims 25, 28 and 31-36 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Applicant's claim to for priority for the EILDV claims in US Application SN 09/029,330 is acknowledged.

4. It is noted that the sequence EILDV is recited in the claims and in numerous instances in the specification, see for example , page 8, line 16, page 9 line 34. The sequence rules embrace all unbranched nucleotide sequences with ten or more bases and all unbranched, non - D amino acid sequences with four or more amino acids. The rules apply to all sequences in a given application, whether claimed or not. All such sequences are relevant for the purposes of building a comprehensive database and properly assessing prior art. It is therefore essential that all sequences, whether only disclosed or also claimed, be included in the database (See MPEP 2421.02. Thus, this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.8821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CF R 1.821 through 1.825 for the reasons(s) set forth on the attached Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

5. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

6. Claims 25, 28 and 31-35 remain rejected and new claim 36 is rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Section 7, pages 3-5.

Applicant argues that the specification (a) provides sufficient guidance to enable the claimed methods because the working examples demonstrate that VLA-4 inhibitors can be used to ameliorate diabetes *in vivo* and specific effective doses ranges and modes of administration of these VLA-4 inhibitors are provided in detail and the Examiner gives no rationale for assuming that this guidance is insufficient, (b) points to a method for determining preferred dosages such that the vast majority of VLA-4 positive cells are coated with the VLA-4 blocking agent, (c) the VLA-4 receptor has been shown to have at least two distinct affinity states and by adjusting the effective concentration of the fibronectin/toxin fusion, it is possible to selectively target pathogenic cells, leaving resting cells substantially unaffected.

The arguments have been considered but have not been found persuasive because (a') the working examples are not drawn to the treatment of insulin-dependent diabetes *in vivo* but rather to adoptive transfers and the delay of onset of insulin-dependent diabetes. In the absence of working examples drawn to the invention as claimed, the general teachings of ranges and modes of administration are not sufficient to enable the claims, especially in view of the specific statement in the specification that there has been little success in treating human diabetes on page 4. Further, even if the working examples were to be drawn to the treatment of insulin-dependent diabetes, the working examples are not drawn to fibronectin but

to other agents. It cannot be determined, given the information in the specification, that fibronectin will function as claimed based on information from antibodies and VCAM constructs when it is not clear that the antibodies and VCAM bind the same way to VLA-4, bind at the same docking site, bind with the same affinity or avidity. Further, Applicant has not addressed the issues raised drawn to pharmacokinetics of soluble fibronectin, (b') as previously discussed, and as Applicant suggests, a dosage in the suggested range would lead to the masking and prevention of binding to all VLA-4 expressing cells which would result in a general immunosuppression and it cannot be predicted how a general immunosuppression would treat insulin dependent diabetes, (c') the specification does not teach methods of determining the appropriate dosages in order to selectively target pathogenic cells, Applicant does not define the term "substantially". Applicant's arguments have not been found persuasive and the rejection is maintained.

7. Claims 25, 28 and 31-35 remain rejected and new claim 36 is rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Section , pages 5-7.

Because applicant did not distinctly and specifically point out the supposed errors in the rejection, the rejection is maintained.

8. Claims 31 and 32 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Section 9, pages 8-9.

Applicant argues that Examiner has not provided specific arguments as to why one would expect that addition of another moiety would destroy the activity of

the chimeric molecule since it is known in the art that moieties can be combined together to form other molecules.

The argument has been considered but has not been found persuasive because the rejection was not drawn to the issue of attachment of another moiety which would destroy the activity of the chimeric molecule, but rather was drawn to the lack of teaching of how to make a chimeric molecule so that it would function as claimed and how to use a chimeric molecule that would not function as claimed. For the reasons previously set forth, the invention as claimed is not enabled. Applicant's arguments have not been found persuasive and the rejection is maintained.

9. Claims 31 and 32 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 10, Section 10, pages 10-11.

Applicant argues that since the term is generic to a class of molecules that the claim is broad but not indefinite. The argument has been considered but has not been found persuasive because although the term is generic to a class of molecules, as previously states, the exact meaning of the word chimeric is unknown. The specification does not provide a standard for ascertaining what is defined as "chimeric" and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. Claims 25, 28 and 31-36 are rejected under 35 USC 112 second paragraph as indefinite because claim 25, in the preamble, recites a method of treating insulin-dependent diabetes. The claims are confusing because although the preamble

recites a method of treating insulin-dependent diabetes, the method steps are drawn to treatment of mammals who do not have diabetes.

11. Claims 25, 28 and 31-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the interests of compact prosecution, because of the indefinite nature of the claim language, see above, issues of scope will also be addressed in this rejection because, if Applicant were to be able to overcome the enablement rejections above, claims 25-28 and 31-36 would still be rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a prophylactic method of delaying insulin dependent diabetes in an individual with a genetic predisposition for diabetes but no beta cell destruction, does not reasonably provide enablement for a method for the treatment of insulin dependent diabetes comprising administering soluble fibronectin polypeptide to a prediabetic mammal or a mammal having partial beta cell destruction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. .

The claims are drawn to a method for the treatment of insulin dependent diabetes comprising administering to a prediabetic mammal or a mammal having partial beta cell destruction a composition comprising a soluble fibronectin polypeptide in an amount effective to treat diabetes. This includes the treatment of diabetes in mammals, humans, that don't have diabetes. The specification teaches

that there has been little success in treating human diabetes and there is a need for immunosuppressive components for use in the prediabetic stage (page 4). The specification teaches that female NOD mice are diabetic at 13-20 weeks (page 16). The specification exemplifies the delayed onset of diabetes in NOD mice with an anti-VLA-4 antibody wherein the antibody is administered at four weeks (see Example 4, page 23).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not teach how to treat insulin dependent diabetes. The *in vivo* data presented is not drawn to treating mammals with diabetes. Examples 1, 3 and 5 are drawn to adoptive transfer experiments wherein spleen cells from NOD mice which have developed diabetes are pretreated with antibodies against VLA-4 or a VCAM construct and then transferred into NOD 8 week old **non-diabetic mice** (emphasis added). The experiments are clearly not commensurate in scope with the claimed invention. Further, even if the claims were to be amended to recite a method of preventing or delaying onset of diabetes (a method to which the specification appears to be drawn), these examples would still not be commensurate in scope with the claimed invention because no mammal develops diabetes by the injection of diabetic spleen cells and one would not expect that protection from or delay of onset would be effected by coating those spleen cells with antibodies or VCAM constructs. Example 4 demonstrates the effects of anti-VLA-4 antibody treatment on a spontaneous diabetes model. A review of Figure 6 clearly demonstrates that treatment is begun at four weeks post partum. The specification clearly teaches that female NOD mice are diabetic at about 13-20

weeks. Clearly, the NOD mice injected were not diabetic. Even if the claims were to be amended to recite a method of preventing or delaying onset of diabetes in prediabetic mammals or mammals with partial destruction of beta cells, Example 4 would still not be commensurate in scope with the claimed invention because, as discussed by Cohen et al, NOD mice do not exhibit beta cell destruction at 4 weeks. Cohen et al (Autoimmune Disease Models, A Guidebook, Academic Press, San Diego, 1994) specifically teach that at 3-4 weeks of age, infiltrating cells surround the blood vessels of the islets of NOD pancreas but that the islets are still clear. At 6-7 weeks, the infiltrating cells reach the islets surrounding them or accumulating at one pole and that between 10-12 weeks, the infiltrating cells penetrate the islets (p. 150). Even if the claims were to be amended to recite a method of preventing or delaying onset of diabetes, this example would still not be commensurate in scope with the claimed invention because it is clear that, since the infiltrating cells do not penetrate the islets at 4 weeks, that the exemplification is not drawn to mammals with partial beta cell destruction. It is noted that as defined in the specification, a prediabetic mammal is one at any stage in the disease process prior to overt diabetes or diabetes onset (p. 7, lines 15-20). As broadly defined, prediabetic mammals include those with partial beta cell destruction.

Further, the specification admits on the record that there has been little success in treating human diabetes and there is a need for immunosuppressive components for use in the prediabetic stage. Given the lack of working examples and the lack of guidance drawn to the claimed invention, it could not be predicted that the invention as claimed would treat insulin-dependent diabetes. In addition,

the difficulties in treating human diabetes, acknowledged by Applicant in the specification is well known in the art. For example, Tisch et al (PNAS, 1994, 91: 437-438) specifically teach that insulin-dependent diabetes is a T-cell-mediated autoimmune disease. Tisch et al specifically state that the most critical factor in treating autoimmune disease is whether the therapy can be used to treat an ongoing autoimmune response or whether it is effective only in terms of prevention. (It is clear that there has been no demonstration in the specification that the method as claimed would be effective to treat ongoing insulin-dependent diabetes) Typically, an autoimmune disease is diagnosed at a time when significant tissue damage has already occurred. At this point, the need is for a form of therapy that can prevent further tissue damage and eliminate or block all or nearly all autoreactive T cells (para bridging columns 2 and 3). Tisch et al further point to the difficulty in treating insulin-dependent diabetes because it is known that T-cells have been activated against as many as six to eight autoantigens and the critical inciting autoantigens are not known (column 3). In view of the known lack of success in treating insulin-dependent diabetes and the critical requirement of determining whether a treatment can be used to treat an ongoing autoimmune response as taught by Tisch et al, it cannot be predicted, based on the information in the specification and the art, that the invention will function as claimed.

Further, even if the claims were to be amended to recite a method of preventing or delaying the onset of insulin-dependent diabetes, the claims would still not be enabled because it is well known in the art that although NOD mice are known as a mouse model for type 1 diabetes, as taught by Atkinson et al (Nature

Medicine, 1999, 5:601-604) when NOD mice are used as a surrogate for humans, genus-specific differences that restrict the interpretation of results of experiments are unavoidable (p. 601, col 1). In NOD mice, type 1 diabetes development is well-choreographed when all the relevant environmental factors are held constant. Specific windows can be defined in which an immunomodulator can be either protective or destructive In contrast, the natural history of type 1 diabetes in humans is such that the age of disease onset is extremely broad, symptoms may occur at any time from the first years of life to well beyond 50 years of age. Atkinson et al further caution that studies analyzing therapeutic agents aimed at preventing type 1 diabetes in NOD mice must be carefully assessed for their functional as well as their practical applicability to therapeutic intervention in human disease. For example, agents used in NOD mice from birth may not be applicable to treatment of humans identified immediately before the onset of type 1 diabetes. It is clear that the genus-unique and strain-specific aspects of diabetogenesis in NOD mice must be fully understood and appreciated if we are to know which therapeutic protocols are reasonable to extrapolate to humans and which are not (p. 603, cols 1 and 2). Although as of early 1999, more than 125 individual methods for the prevention or delay of type 1 diabetes in NOD mice had been reported (para bridging pages 602-603), Atkinson et al teach that it is clear that the course of type 1 diabetes development in randomly breeding humans will not be as easily deviated as it is in highly inbred rodent models in which genetic risk is a constant such that interventions can be initiated at very early stages of pathogenesis (p. 604, col 2). Finally, even if it were to be demonstrated that fibronectin polypeptides were

effective at delaying or preventing onset of diabetes in NOD mice, the specification does not teach, give guidance on or provide working examples that would provide guidance to one of skill in the art as to when fibronectin should be administered to the broadly claimed mammals. Clearly, as taught by Atkinson et al, the age of onset of human diabetes ranges from the first years of life to well beyond fifty years of age. Further, although it is known that there is a population of human mammals at risk for developing type 1 diabetes, it is also known that not all of the members of that population develop the disease and it cannot be predicted which member of that population will develop the disease because of the genetic and environmental heterogeneity associated with the natural history of the disease. In comparing the heterogeneous human population with NOD mice, Atkinson et al specifically states that there is little evidence that many of the individuals at high risk for type 1 diabetes development would have a set of immune deficiencies that would prove as malleable as those of the highly inbred NOD mouse rodent population (p. 603, col 1). As taught by Bowman et al (Immunology Today, 1994, Vol 15:115-120), given the genetic heterogeneity within the human population, the development of insulin-dependent diabetes is likely to reflect heterogeneous mixtures of susceptibility genes whose penetrances are responsive to different thresholds of intragenic and environmental influences and that given these complexities it has thus been difficult for clinical investigators to develop diagnostic tools for the early identification of humans destined to develop insulin-dependent diabetes (p. 115, col 2). The specification provides no information on or guidance on how to determine which

mammal could receive benefit from the method. It is clear that the specification does not teach how to use the method as claimed.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to practice the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

12. Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 36 is drawn to a fibronectin polypeptide that contains an alternatively spliced non-type III connecting segment of fibronectin. This includes any alternatively spliced non-type III connecting segment. The specification teaches that blocking agents may include fibronectin having an alternatively spliced non-type III connecting segment (p. 8, lines 15-16).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not teach how to make the alternatively spliced non-type III connecting segment so that it will function as claimed. It is well known in the art that alternative splicing produces products with different amino acid constituents whereby additions to, truncations or deletion of amino acids of the protein product are produced. However, applicant has not enabled all of these

types of modified connecting segments because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Burgess et al. J of Cell Bio. 111:2129-2138, 1990. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Lazar et al. Molecular and Cellular Biology 8:1247-1252 (1988). Similarly it has been shown that a glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies. See Tao et al., The Journal of Immunology, 143:2595-2601 (1989). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Further, the specification fails to teach what deletions, truncations, substitutions can be tolerated that will allow the alternatively spliced non-type III connecting segment of fibronectin to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions

can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (see Bowie et al (Science, 247:1306-1310, 1990, p. 1306, col.2). Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

13. All other objections and rejections recited in Paper No. 10 are withdrawn.

14. No claims allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

16. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

17. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

18. Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Susan Ungar
Primary Patent Examiner
March 2, 2001

Appl tion No. 09/234,290

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☑ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☑ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☑ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☑ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☑ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☑ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.